

**(19) World Intellectual Property Organization
International Bureau**



A standard linear barcode representing the document's unique identifier.

**(43) International Publication Date
30 November 2006 (30.11.2006)**

PCT

(10) International Publication Number
WO 2006/126947 A1

(51) **International Patent Classification:**
C07D 211/44 (2006.01) *C07D 211/26* (2006.01)
A61K 31/445 (2006.01) *A61P 17/00* (2006.01)
A61K 31/4545 (2006.01) *A61P 19/00* (2006.01)
A61P 11/06 (2006.01)

(21) **International Application Number:**
PCT/SE2006/000611

(22) **International Filing Date:** 24 May 2006 (24.05.2006)

(25) **Filing Language:** English

(26) **Publication Language:** English

(30) **Priority Data:**
0501212-5 27 May 2005 (27.05.2005) SE

(71) **Applicant (for all designated States except US):** ASTRAZENECA AB [SE/SE]; S-151 85 Södertälje (SE).

(72) **Inventors; and**

(75) **Inventors/Applicants (for US only):** PERRY, Matthew [GB/GB]; AstraZeneca R & D Charnwood, Bakewell Road, Loughborough, Leicestershire LE11 5RH (GB). SPRINGTHORPE, Brian [GB/GB]; AstraZeneca R & D Charnwood, Bakewell Road, Loughborough, Leicestershire LE11 5RH (GB).

(74) **Agent:** ASTRAZENECA; Global Intellectual Property, S-151 85 Södertälje (SE).

(81) **Designated States (unless otherwise indicated, for every kind of national protection available):** AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) **Designated States (unless otherwise indicated, for every kind of regional protection available):** ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— with international search report

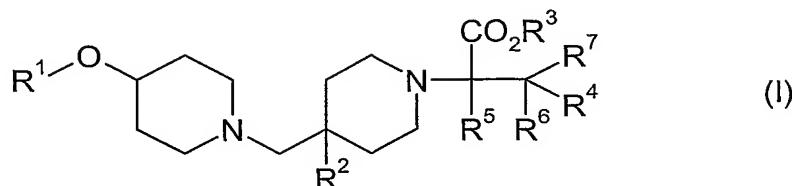
For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

Published:

— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PIPERIDINES FOR THE TREATMENT OF CHEMOKINE MEDIATED DISEASES



(57) Abstract: The present invention provides a compound of a formula (I); wherein the variables are defined herein; to a process for preparing such a compound; and to the use of such a compound in the treatment of a chemokine (such as CCR3) or H1 mediated disease state.

Piperidines for the treatment of chemokine mediated diseases.

The present invention concerns piperidine derivatives having pharmaceutical activity, to processes for preparing such derivatives, to pharmaceutical compositions comprising such derivatives and to the use of such derivatives as active therapeutic agents.

Pharmaceutically active piperidine derivatives are disclosed in WO 2004/087659.

Histamine is a basic amine, 2-(4-imidazolyl)-ethylamine, and is formed from histidine by histidine decarboxylase. It is found in most tissues of the body, but is present in high concentrations in the lung, skin and in the gastrointestinal tract. At the cellular level inflammatory cells such as mast cells and basophils store large amounts of histamine. It is recognised that the degranulation of mast cells and basophils and the subsequent release of histamine is a fundamental mechanism responsible for the clinical manifestation of an allergic process. Histamine produces its actions by an effect on specific histamine G-protein coupled receptors, which are of four main types, H1, H2, H3, and H4. Histamine H1 antagonists comprise the largest class of medications used in the treatment of patients with allergic disorders, for example rhinitis or urticaria. H1 antagonists are useful in controlling the allergic response by for example blocking the action of histamine on post-capillary venule smooth muscle, resulting in decreased vascular permeability, exudation and oedema. The antagonists also produce blockade of the actions of histamine on the H1 receptors on c-type nociceptive nerve fibres, resulting in decreased itching and sneezing.

Chemokines are chemotactic cytokines that are released by a wide variety of cells to attract macrophages, T cells, eosinophils, basophils and neutrophils to sites of inflammation and also play a rôle in the maturation of cells of the immune system. Chemokines play an important rôle in immune and inflammatory responses in various diseases and disorders, including asthma and allergic diseases, as well as autoimmune pathologies such as rheumatoid arthritis and atherosclerosis. These small secreted molecules are a growing superfamily of 8-14 kDa proteins characterised by a conserved four cysteine motif. The chemokine superfamily can be divided into two main groups exhibiting characteristic structural motifs, the Cys-X-Cys (C-X-C, or α) and Cys-Cys (C-C, or β) families. These are distinguished on the basis of a single amino acid insertion between the NH-proximal pair of cysteine residues and sequence similarity.

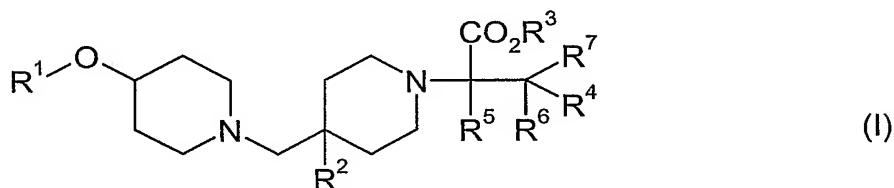
The C-X-C chemokines include several potent chemoattractants and activators of neutrophils such as interleukin-8 (IL-8) and neutrophil-activating peptide 2 (NAP-2).

The C-C chemokines include potent chemoattractants of monocytes and lymphocytes but not neutrophils such as human monocyte chemotactic proteins 1-3 (MCP-1, MCP-2 and MCP-3), RANTES (Regulated on Activation, Normal T Expressed and Secreted), eotaxin and the macrophage inflammatory proteins 1 α and 1 β (MIP-1 α and MIP-1 β).

Studies have demonstrated that the actions of the chemokines are mediated by subfamilies of G protein-coupled receptors, among which are the receptors designated CCR1, CCR2, CCR2A, CCR2B, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10, CXCR1, CXCR2, CXCR3 and CXCR4. These receptors represent good targets for drug development since agents which modulate these receptors would be useful in the treatment of disorders and diseases such as those mentioned above.

Viral infections are known to cause lung inflammation. It has been shown experimentally that the common cold increases mucosal output of eotaxin in the airways. Instillation of eotaxin into the nose can mimic some of the signs and symptoms of a common cold. (See, Greiff L *et al* Allergy (1999) 54(11) 1204-8 [Experimental common cold increase mucosal output of eotaxin in atopic individuals] and Kawaguchi M *et al* Int. Arch. Allergy Immunol. (2000) 122 S1 44 [Expression of eotaxin by normal airway epithelial cells after virus A infection].)

The present invention provides a compound of formula (I):



wherein:

R¹ is phenyl optionally substituted by halogen, cyano, C₁₋₄ alkyl or C₁₋₄ alkoxy;

R² is hydrogen or hydroxy;

R³ is hydrogen, C₁₋₆ alkyl or phenyl(C₁₋₄ alkyl); wherein phenyl is optionally substituted with halogen, hydroxy, nitro, S(O)_q(C₁₋₄ alkyl), S(O)₂NH₂, S(O)₂NH(C₁₋₄ alkyl), S(O)₂N(C₁₋₄ alkyl)₂, cyano, C₁₋₄ alkyl, C₁₋₄ alkoxy, C(O)NH₂, C(O)NH(C₁₋₄ alkyl), C(O)N(C₁₋₄ alkyl)₂, CO₂H, CO₂(C₁₋₄ alkyl), NHC(O)(C₁₋₄ alkyl), NHS(O)₂(C₁₋₄ alkyl), C(O)(C₁₋₄ alkyl), CF₃ or OCF₃;

q is 0, 1 or 2;

R⁴ is methyl, CH(CH₃)₂, or C₃₋₇ cycloalkyl optionally substituted by C₁₋₄ alkyl;

R⁵, R⁶ and R⁷ are, independently, hydrogen or methyl;

or R⁴ and R⁵ join to form a 3-7 membered carbocyclic ring optionally substituted by C₁₋₄ alkyl; and two of the ring carbons of this ring can be joined through a 1 or 2 carbon alkylene chain (which is itself optionally substituted by C₁₋₄ alkyl) such that a bicyclic ring system is formed;

or a N-oxide thereof; or a pharmaceutically acceptable salt thereof.

Certain compounds of the present invention can exist in different isomeric forms (such

as enantiomers, diastereomers, geometric isomers or tautomers). The present invention covers all such isomers and mixtures thereof in all proportions.

The compounds of the invention can be zwitterionic and all such zwitterions are within the invention.

Pharmaceutically acceptable salts include acid addition salts such as a hydrochloride, dihydrochloride, hydrobromide, phosphate, sulfate, acetate, diacetate, fumarate, maleate, malonate, succinate, tartrate, citrate, oxalate, methanesulfonate or *p*-toluenesulfonate.

Pharmaceutically acceptable salts also include an alkali metal (for example sodium or potassium) or alkaline earth metal (for example magnesium or calcium) salt of a compound of formula (I) wherein R³ is hydrogen. A pharmaceutically acceptable salt is, for example, a hemi-salt. In the neutral state a hemi-salt is formed by two compounds of formula (I), wherein R³ is hydrogen, and one alkaline earth metal (for example calcium).

The compounds of the invention may exist as solvates (such as hydrates) and the present invention covers all such solvates.

Halogen includes fluorine, chlorine, bromine and iodine. Halogen is, for example, fluorine or chlorine.

Alkyl is straight or branched chain and is, for example, methyl, ethyl, n-propyl, iso-propyl or tert-butyl.

Cycloalkyl is, for example, cyclopropyl, cyclopentyl or cyclohexyl.

In one particular aspect the present invention provides a compound of formula (I) wherein: R¹ is phenyl optionally substituted by halogen, cyano, C₁₋₄ alkyl or C₁₋₄ alkoxy; R² is hydrogen or hydroxy; R³ is hydrogen, C₁₋₆ alkyl or phenyl(C₁₋₄ alkyl); wherein phenyl is optionally substituted with halogen, hydroxy, nitro, S(O)_q(C₁₋₄ alkyl), S(O)₂NH₂,

S(O)₂NH(C₁₋₄ alkyl), S(O)₂N(C₁₋₄ alkyl)₂, cyano, C₁₋₄ alkyl, C₁₋₄ alkoxy, C(O)NH₂, C(O)NH(C₁₋₄ alkyl), C(O)N(C₁₋₄ alkyl)₂, CO₂H, CO₂(C₁₋₄ alkyl), NHC(O)(C₁₋₄ alkyl), NHS(O)₂(C₁₋₄ alkyl), C(O)(C₁₋₄ alkyl), CF₃ or OCF₃; q is 0, 1 or 2; R⁴ is CH(CH₃)₂, or C₃₋₇ cycloalkyl optionally substituted by C₁₋₄ alkyl; R⁵ is hydrogen; R⁶ and R⁷ are both
5 hydrogen; or R⁴ and R⁵ join to form a 3-7 membered carbocyclic ring optionally substituted by C₁₋₄ alkyl; and two of the ring carbons of this ring can be joined through a 1 or 2 carbon alkylene chain (which is itself optionally substituted by C₁₋₄ alkyl) such that a bicyclic ring system is formed; or a N-oxide thereof; or a pharmaceutically acceptable salt thereof.

10 In a further aspect the present invention provides a compound of formula (I) wherein R¹ is phenyl optionally substituted (for example with two or three of the same or different) with fluorine, chlorine, cyano, C₁₋₄ alkyl (for example methyl) or C₁₋₄ alkoxy (for example methoxy).

15 In another aspect the present invention provides a compound wherein R¹ is phenyl optionally substituted (for example with two or three of the same or different) with fluorine, chlorine, cyano or C₁₋₄ alkyl (for example methyl).

In yet another aspect the present invention provides a compound wherein R¹ is phenyl substituted by two or three substituents independently selected from: fluorine, chlorine, cyano and methyl.

20 In yet another aspect the present invention provides a compound wherein R¹ is phenyl substituted by two or three substituents independently selected from: fluorine, chlorine and methyl.

25 In a further aspect the present invention provides a compound wherein R¹ is phenyl substituted by two or three substituents independently selected from: chlorine and methyl. For example R¹ is 3,4-dichlorophenyl, 2,4-dichloro-3-methylphenyl or 3,4-dichloro-2-methylphenyl. R¹ can also be 4-chloro-2-methylphenyl or 4-fluoro-2-methylphenyl.

In a still further aspect the present invention provides a compound wherein R² is hydrogen.

30 In another aspect the present invention provides a compound wherein R³ is hydrogen or C₁₋₆ alkyl (for example methyl or ethyl).

In yet another aspect the present invention provides a compound wherein R³ is hydrogen.

In a further aspect the present invention provides a sodium or potassium salt of a compound of formula (I) wherein R³ is hydrogen.

In a still further aspect the present invention provides a compound wherein R⁴ is CH(CH₃)₂.

5 In another aspect the present invention provides a compound wherein R⁴ is C₃₋₇ cycloalkyl optionally substituted by C₁₋₄ alkyl.

In a further aspect the present invention provides a compound wherein R⁴ is C₃₋₆ cycloalkyl (for example cyclopropyl, cyclopentyl or cyclohexyl).

10 In a still further aspect the present invention provides a compound wherein R⁵ is hydrogen.

In a further aspect the present invention provides a compound wherein R⁵ is methyl.

In another aspect the present invention provides a compound wherein R⁴ and R⁵ join to form a 3-7 membered ring (for example a cyclohexyl or cyclopentyl ring).

15 In yet another aspect the present invention provides a compound wherein R⁴ and R⁵ join to form a 3-7 membered ring and two of the ring carbons of this ring join through a 1 or 2 carbon alkylene chain such that a bicyclic ring system (for example a bicyclo[2.2.1]heptane ring system).

In a further aspect the present invention provides a compound wherein R⁶ and R⁷ are both hydrogen.

20 In another aspect the present invention provides a compound wherein R², R⁶ and R⁷ are all hydrogen; R⁵ is methyl; and R⁴ is CH(CH₃)₂.

25 In yet another aspect the present invention provides a compound wherein R¹ is phenyl optionally substituted by halogen (for example chloro or fluoro) or C₁₋₄ alkyl (for example methyl); R² is hydrogen; R³ is hydrogen, C₁₋₆ alkyl (for example methyl); R⁴ is methyl, CH(CH₃)₂, or C₃₋₇ cycloalkyl (for example cyclopropyl, cyclopentyl or cyclohexyl); R⁵ is hydrogen or methyl; or R⁴ and R⁵ join to form a 3-7 membered carbocyclic ring (for example cyclopentyl or cyclohexyl); R⁶ is hydrogen or methyl; and R⁷ is hydrogen.

30 In a still further aspect the present invention provides a compound of formula (I) wherein: R¹ is phenyl optionally substituted by halogen (for example chloro) or C₁₋₄ alkyl (for example methyl); R² is hydrogen; R³ is hydrogen or C₁₋₆ alkyl (for example methyl); R⁴ is CH(CH₃)₂, or C₃₋₇ cycloalkyl (for example cyclopropyl, cyclopentyl or cyclohexyl);

R⁵ is hydrogen; or R⁴ and R⁵ join to form a 3-7 membered carbocyclic ring (for example cyclopentyl or cyclohexyl); and two of the ring carbons of this ring can be joined through a 1 or 2 carbon alkylene chain such that a bicyclic ring system (for example a bicyclo[2.2.1]heptane ring system) is formed.

5 A compound of formula (I) that is:

(2S)-3-Cyclohexyl-2-(4-{[4-(3,4-dichloro-2-methylphenoxy)piperidin-1-yl]methyl}piperidin-1-yl)propanoic acid;

(2S)-3-Cyclohexyl-2-(4-{[4-(3,4-dichloro-2-methylphenoxy)piperidin-1-yl]methyl}piperidin-1-yl)propanoic acid;

10 (2S)-3-Cyclopropyl-2-(4-{[4-(3,4-dichloro-2-methylphenoxy)piperidin-1-yl]methyl}piperidin-1-yl)propanoic acid;

(2S)-3-Cyclopentyl-2-(4-{[4-(3,4-dichlorophenoxy)piperidin-1-yl]methyl}piperidin-1-yl)propanoic acid;

15 3-Cyclopentyl-2-{4-[4-(3,4-dichloro-2-methyl-phenoxy)-piperidin-1-ylmethyl]-piperidin-1-yl}-propionic acid;

1-(4-{[4-(3,4-Dichlorophenoxy)piperidin-1-yl]methyl}piperidin-1-yl)cyclohexanecarboxylic acid;

1-(4-{[4-(3,4-Dichloro-2-methylphenoxy)piperidin-1-yl]methyl}piperidin-1-yl)cyclohexanecarboxylic acid;

20 1-(4-{[4-(3,4-Dichloro-2-methylphenoxy)piperidin-1-yl]methyl}piperidin-1-yl)cyclopentanecarboxylic acid;

(2S)-2-{4-[4-(3,4-Dichloro-2-methyl-phenoxy)-piperidin-1-ylmethyl]-piperidin-1-yl}-4-methyl-pentanoic acid;

25 2-{4-[4-(3,4-Dichloro-phenoxy)-piperidin-1-ylmethyl]-piperidin-1-yl}-4-methyl-pentanoic acid;

2-{4-[4-(4-Chloro-2-methyl-phenoxy)-piperidin-1-ylmethyl]-piperidin-1-yl}-3-methyl-butrylic acid;

1-{4-[4-(4-Fluoro-2-methyl-phenoxy)-piperidin-1-ylmethyl]-piperidin-1-yl}-cyclohexanecarboxylic acid;

30 1-(4-{[4-(4-Chloro-2-methylphenoxy)piperidin-1-yl]methyl}piperidin-1-yl)cyclohexanecarboxylic acid;

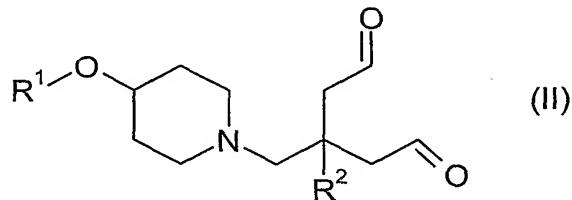
(2*S*)-2-(4-{[4-(3,4-Dichlorophenoxy)piperidin-1-yl]methyl}piperidin-1-yl)-3-methylbutanoic acid;

(2*S*)-2-{4-[4-(3,4-Dichloro-2-methyl-phenoxy)-piperidin-1-ylmethyl]-piperidin-1-yl}-2,4-dimethyl-pentanoic acid; or,

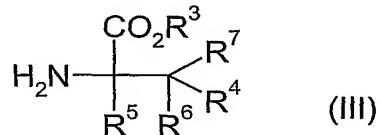
5 (2*S*)-2-{4-[4-(4-Chloro-2-methyl-phenoxy)-piperidin-1-ylmethyl]-piperidin-1-yl}-2,4-dimethyl-pentanoic acid;
or a pharmaceutically acceptable salt thereof.

The compounds of the present invention can be prepared as described below or by methods analogous to those described in WO 2004/087659.

10 A compound of formula (I) can be prepared by reacting a compound of formula (II):



with a compound of formula (III):



15 in the presence of NaBH(OAc)₃ or NaBH₃(CN) in a suitable solvent (for example an aliphatic alcohol such as methanol or ethanol) at a suitable temperature (such as in the range 0°C to 30°C).

Alternatively, a compound of formula (I), where R³ is alkyl or phenylalkyl, can be prepared by reacting a compound of formula (II) with a compound of formula (III), where R³ is alkyl or phenylalkyl, in the presence of NaBH(OAc)₃ in the presence of a suitable base (such as a tertiary amine, for example Hünigs base or triethylamine) in a suitable solvent (such as tetrahydrofuran) at a suitable temperature (such as in the range 0°C to 30°C).

For a compound of formula (I):

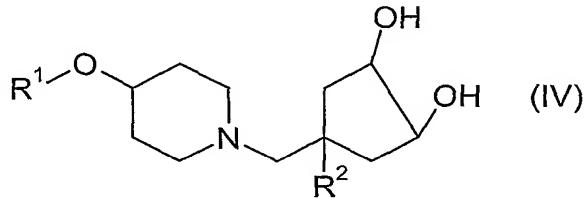
- when R³ is hydrogen said compound may be converted to a compound of the invention where R³ is not hydrogen by a standard esterification or salt formation method well known in the art; and,

- when R³ is not hydrogen said compound may be converted to a compound of the invention where R³ is hydrogen by a standard ester hydrolysis or acidification method well known in the art.

Such methods are described in undergraduate organic chemistry textbooks (such as

5 Advanced Organic Chemistry by J March, 5th edition M B Smith and J March, Wiley, 2001).

A compound of formula (II) can be prepared by reacting a compound of formula (IV):



10 with lead tetra-acetate in the presence of sodium carbonate in dichloromethane, or by sodium periodate in water.

The preparations of various phenoxy piperidines and other intermediates are described in the literature and WO 2004/087659.

15 In the above processes it may be desirable or necessary to protect an acid group or a hydroxy or other potentially reactive group. Suitable protecting groups and details of processes for adding and removing such groups may be found in "Protective Groups in Organic Synthesis", 3rd Edition (1999) by Greene and Wuts.

In another aspect the present invention provides processes for the preparation of compounds of formula (I).

20 The compounds of formula (I) have activity as pharmaceuticals, in particular as modulators of chemokine receptor (for example CCR3) activity, and may be used in the treatment of autoimmune, inflammatory, proliferative or hyperproliferative diseases, or immunologically-mediated diseases (including rejection of transplanted organs or tissues and Acquired Immunodeficiency Syndrome (AIDS)).

25 Examples of these conditions are:

- respiratory tract: obstructive diseases of the airways including: asthma, including bronchial, allergic, intrinsic, extrinsic, exercise-induced, drug-induced (including aspirin and NSAID-induced) and dust-induced asthma, both intermittent and persistent and of all

severities, and other causes of airway hyper-responsiveness; chronic obstructive pulmonary disease (COPD); bronchitis, including infectious and eosinophilic bronchitis; emphysema; bronchiectasis; cystic fibrosis; sarcoidosis; farmer's lung and related diseases; hypersensitivity pneumonitis; lung fibrosis, including cryptogenic fibrosing alveolitis,

5 idiopathic interstitial pneumonias, fibrosis complicating anti-neoplastic therapy and chronic infection, including tuberculosis and aspergillosis and other fungal infections; complications of lung transplantation; vasculitic and thrombotic disorders of the lung vasculature, and pulmonary hypertension; antitussive activity including treatment of chronic cough associated with inflammatory and secretory conditions of the airways, and
10 iatrogenic cough; acute and chronic rhinitis including rhinitis medicamentosa, and vasomotor rhinitis; perennial and seasonal allergic rhinitis including rhinitis nervosa (hay fever); nasal polypsis; acute viral infection including the common cold, and infection due to respiratory syncytial virus, influenza, coronavirus (including SARS) or adenovirus; or eosinophilic esophagitis;

15 2. bone and joints: arthritides associated with or including osteoarthritis/osteoarthrosis, both primary and secondary to, for example, congenital hip dysplasia; cervical and lumbar spondylitis, and low back and neck pain; osteoporosis; rheumatoid arthritis and Still's disease; seronegative spondyloarthropathies including ankylosing spondylitis, psoriatic arthritis, reactive arthritis and undifferentiated spondarthropathy; septic arthritis and other
20 infection-related arthropathies and bone disorders such as tuberculosis, including Potts' disease and Poncet's syndrome; acute and chronic crystal-induced synovitis including urate gout, calcium pyrophosphate deposition disease, and calcium apatite related tendon, bursal and synovial inflammation; Behcet's disease; primary and secondary Sjogren's syndrome; systemic sclerosis and limited scleroderma; systemic lupus erythematosus, mixed
25 connective tissue disease, and undifferentiated connective tissue disease; inflammatory myopathies including dermatomyositis and polymyositis; polymalgia rheumatica; juvenile arthritis including idiopathic inflammatory arthritides of whatever joint distribution and associated syndromes, and rheumatic fever and its systemic complications; vasculitides including giant cell arteritis, Takayasu's arteritis, Churg-Strauss syndrome, polyarteritis
30 nodosa, microscopic polyarteritis, and vasculitides associated with viral infection, hypersensitivity reactions, cryoglobulins, and paraproteins; low back pain; Familial

Mediterranean fever, Muckle-Wells syndrome, and Familial Hibernian Fever, Kikuchi disease; drug-induced arthalgias, tendonitides, and myopathies;

3. pain and connective tissue remodelling of musculoskeletal disorders due to injury [for example sports injury] or disease: arthritides (for example rheumatoid arthritis,

5 osteoarthritis, gout or crystal arthropathy), other joint disease (such as intervertebral disc degeneration or temporomandibular joint degeneration), bone remodelling disease (such as osteoporosis, Paget's disease or osteonecrosis), polychondritis, scleroderma, mixed connective tissue disorder, spondyloarthropathies or periodontal disease (such as periodontitis);

10 4. skin: psoriasis, atopic dermatitis, contact dermatitis or other eczematous dermatoses, and delayed-type hypersensitivity reactions; phyto- and photodermatitis; seborrhoeic dermatitis, dermatitis herpetiformis, lichen planus, lichen sclerosus et atrophica, pyoderma gangrenosum, skin sarcoid, discoid lupus erythematosus, pemphigus, pemphigoid, epidermolysis bullosa, urticaria, angioedema, vasculitides, toxic erythemas, cutaneous 15 eosinophilias, alopecia areata, male-pattern baldness, Sweet's syndrome, Weber-Christian syndrome, erythema multiforme; cellulitis, both infective and non-infective; panniculitis; cutaneous lymphomas, non-melanoma skin cancer and other dysplastic lesions; drug-induced disorders including fixed drug eruptions;

20 5. eyes: blepharitis; conjunctivitis, including perennial and vernal allergic conjunctivitis; iritis; anterior and posterior uveitis; choroiditis; autoimmune; degenerative or inflammatory disorders affecting the retina; ophthalmitis including sympathetic ophthalmitis; sarcoidosis; infections including viral, fungal, and bacterial;

25 6. gastrointestinal tract: glossitis, gingivitis, periodontitis; oesophagitis, including reflux; eosinophilic gastro-enteritis, mastocytosis, Crohn's disease, colitis including ulcerative colitis, proctitis, pruritis ani; coeliac disease, irritable bowel syndrome, and food-related allergies which may have effects remote from the gut (for example migraine, rhinitis or eczema);

7. abdominal: hepatitis, including autoimmune, alcoholic and viral; fibrosis and cirrhosis of the liver; cholecystitis; pancreatitis, both acute and chronic;

30 8. genitourinary: nephritis including interstitial and glomerulonephritis; nephrotic syndrome; cystitis including acute and chronic (interstitial) cystitis and Hunner's ulcer;

acute and chronic urethritis, prostatitis, epididymitis, oophoritis and salpingitis; vulvo-vaginitis; Peyronie's disease; erectile dysfunction (both male and female);

9. allograft rejection: acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin or cornea or following blood transfusion; or
5 chronic graft versus host disease;

10. CNS: Alzheimer's disease and other dementing disorders including CJD and nvCJD; amyloidosis; multiple sclerosis and other demyelinating syndromes; cerebral atherosclerosis and vasculitis; temporal arteritis; myasthenia gravis; acute and chronic pain (acute, intermittent or persistent, whether of central or peripheral origin) including visceral pain, headache, migraine, trigeminal neuralgia, atypical facial pain, joint and bone pain, pain arising from cancer and tumor invasion, neuropathic pain syndromes including diabetic, post-herpetic, and HIV-associated neuropathies; neurosarcoidosis; central and peripheral nervous system complications of malignant, infectious or autoimmune processes;

15. 11. other auto-immune and allergic disorders including Hashimoto's thyroiditis, Graves' disease, Addison's disease, diabetes mellitus, idiopathic thrombocytopaenic purpura, eosinophilic fasciitis, hyper-IgE syndrome, antiphospholipid syndrome;

12. other disorders with an inflammatory or immunological component; including acquired immune deficiency syndrome (AIDS), leprosy, Sezary syndrome, and
20 paraneoplastic syndromes;

13. cardiovascular: atherosclerosis, affecting the coronary and peripheral circulation; pericarditis; myocarditis , inflammatory and auto-immune cardiomyopathies including myocardial sarcoid; ischaemic reperfusion injuries; endocarditis, valvulitis, and aortitis including infective (for example syphilitic); vasculitides; disorders of the proximal and
25 peripheral veins including phlebitis and thrombosis, including deep vein thrombosis and complications of varicose veins;

14. oncology: treatment of common cancers including prostate, breast, lung, ovarian, pancreatic, bowel and colon, stomach, skin and brain tumors and malignancies affecting the bone marrow (including the leukaemias) and lymphoproliferative systems, such as
30 Hodgkin's and non-Hodgkin's lymphoma; including the prevention and treatment of metastatic disease and tumour recurrences, and paraneoplastic syndromes; or,

15. gastrointestinal tract: Coeliac disease, proctitis, eosinopilic gastro-enteritis, mastocytosis, Crohn's disease, ulcerative colitis, microscopic colitis, indeterminant colitis, irritable bowel disorder, irritable bowel syndrome, non-inflammatory diarrhea, food-related allergies which have effects remote from the gut, e.g., migraine, rhinitis and
5 eczema.

The compounds of formula (I) or a pharmaceutically acceptable salt thereof, are also H1 antagonists (and can, therefore, be used in the treatment of allergic disorders); and may also be used to control a sign and/or symptom of what is commonly referred to as a cold (for example a sign and/or symptom of a common cold or influenza or other associated
10 respiratory virus infection).

According to a further feature of the present invention there is provided a method for treating a chemokine mediated disease state (for example a CCR3 mediated disease state) in a mammal, such as man, suffering from, or at risk of, said disease state, which comprises administering to a mammal in need of such treatment a therapeutically effective
15 amount of a compound of the formula (I) or a pharmaceutically acceptable salt thereof.

According to another feature of the present invention there is provided a method for antagonising H1 in a mammal, such as man, suffering from, or at risk of, an H1 mediated disease state, which comprises administering to a mammal in need of such treatment a therapeutically effective amount of a compound of the formula (I) or a pharmaceutically acceptable salt thereof.
20

According to yet another feature of the present invention there is provided a method for treating a sign and/or symptom of what is commonly referred to as a cold in a mammal, such as man, suffering from, or at risk of, said disease state, which comprises administering to a mammal in need of such treatment a therapeutically effective amount of
25 a compound of the formula (I) or a pharmaceutically acceptable salt thereof.

The invention also provides a compound of the formula (I), or a pharmaceutically acceptable salt thereof, for use in therapy.

In another aspect the invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in
30 therapy (for example modulating chemokine receptor activity (for example CCR3 receptor activity), antagonising H1 or treating a sign and/or symptom of what is commonly referred to as a cold).

The invention further provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of:

1. respiratory tract: obstructive diseases of the airways including: asthma, including bronchial, allergic, intrinsic, extrinsic, exercise-induced, drug-induced (including aspirin and NSAID-induced) and dust-induced asthma, both intermittent and persistent and of all severities, and other causes of airway hyper-responsiveness; chronic obstructive pulmonary disease (COPD); bronchitis, including infectious and eosinophilic bronchitis; emphysema; bronchiectasis; cystic fibrosis; sarcoidosis; farmer's lung and related diseases;
- 5 hypersensitivity pneumonitis; lung fibrosis, including cryptogenic fibrosing alveolitis, idiopathic interstitial pneumonias, fibrosis complicating anti-neoplastic therapy and chronic infection, including tuberculosis and aspergillosis and other fungal infections; complications of lung transplantation; vasculitic and thrombotic disorders of the lung vasculature, and pulmonary hypertension; antitussive activity including treatment of
- 10 chronic cough associated with inflammatory and secretory conditions of the airways, and iatrogenic cough; acute and chronic rhinitis including rhinitis medicamentosa, and vasomotor rhinitis; perennial and seasonal allergic rhinitis including rhinitis nervosa (hay fever); nasal polypsis; acute viral infection including the common cold, and infection due to respiratory syncytial virus, influenza, coronavirus (including SARS) or adenovirus; or
- 15 eosinophilic esophagitis;
- 20 2. bone and joints: arthritides associated with or including osteoarthritis/osteoarthrosis, both primary and secondary to, for example, congenital hip dysplasia; cervical and lumbar spondylitis, and low back and neck pain; osteoporosis; rheumatoid arthritis and Still's disease; seronegative spondyloarthropathies including ankylosing spondylitis, psoriatic arthritis, reactive arthritis and undifferentiated spondarthropathy; septic arthritis and other infection-related arthropathies and bone disorders such as tuberculosis, including Potts' disease and Poncet's syndrome; acute and chronic crystal-induced synovitis including urate gout, calcium pyrophosphate deposition disease, and calcium apatite related tendon, bursal and synovial inflammation; Behcet's disease; primary and secondary Sjogren's syndrome;
- 25 systemic sclerosis and limited scleroderma; systemic lupus erythematosus, mixed connective tissue disease, and undifferentiated connective tissue disease; inflammatory myopathies including dermatomyositis and polymyositis; polymalgia rheumatica; juvenile
- 30

arthritis including idiopathic inflammatory arthritides of whatever joint distribution and associated syndromes, and rheumatic fever and its systemic complications; vasculitides including giant cell arteritis, Takayasu's arteritis, Churg-Strauss syndrome, polyarteritis nodosa, microscopic polyarteritis, and vasculitides associated with viral infection,

5 hypersensitivity reactions, cryoglobulins, and paraproteins; low back pain; Familial Mediterranean fever, Muckle-Wells syndrome, and Familial Hibernian Fever, Kikuchi disease; drug-induced arthralgias, tendonitides, and myopathies;

3. pain and connective tissue remodelling of musculoskeletal disorders due to injury [for example sports injury] or disease: arthritides (for example rheumatoid arthritis, 10 osteoarthritis, gout or crystal arthropathy), other joint disease (such as intervertebral disc degeneration or temporomandibular joint degeneration), bone remodelling disease (such as osteoporosis, Paget's disease or osteonecrosis), polychondritis, scleroderma, mixed connective tissue disorder, spondyloarthropathies or periodontal disease (such as periodontitis);

15 4. skin: psoriasis, atopic dermatitis, contact dermatitis or other eczematous dermatoses, and delayed-type hypersensitivity reactions; phyto- and photodermatitis; seborrhoeic dermatitis, dermatitis herpetiformis, lichen planus, lichen sclerosus et atrophica, pyoderma gangrenosum, skin sarcoid, discoid lupus erythematosus, pemphigus, pemphigoid, epidermolysis bullosa, urticaria, angioedema, vasculitides, toxic erythemas, cutaneous 20 eosinophilias, alopecia areata, male-pattern baldness, Sweet's syndrome, Weber-Christian syndrome, erythema multiforme; cellulitis, both infective and non-infective; panniculitis; cutaneous lymphomas, non-melanoma skin cancer and other dysplastic lesions; drug-induced disorders including fixed drug eruptions;

25 5. eyes: blepharitis; conjunctivitis, including perennial and vernal allergic conjunctivitis; iritis; anterior and posterior uveitis; choroiditis; autoimmune; degenerative or inflammatory disorders affecting the retina; ophthalmitis including sympathetic ophthalmitis; sarcoidosis; infections including viral, fungal, and bacterial;

6. gastrointestinal tract: glossitis, gingivitis, periodontitis; oesophagitis, including reflux; 30 eosinophilic gastro-enteritis, mastocytosis, Crohn's disease, colitis including ulcerative colitis, proctitis, pruritis ani; coeliac disease, irritable bowel syndrome, and food-related allergies which may have effects remote from the gut (for example migraine, rhinitis or eczema);

7. abdominal: hepatitis, including autoimmune, alcoholic and viral; fibrosis and cirrhosis of the liver; cholecystitis; pancreatitis, both acute and chronic;
8. genitourinary: nephritis including interstitial and glomerulonephritis; nephrotic syndrome; cystitis including acute and chronic (interstitial) cystitis and Hunner's ulcer;
- 5 acute and chronic urethritis, prostatitis, epididymitis, oophoritis and salpingitis; vulvo-vaginitis; Peyronie's disease; erectile dysfunction (both male and female);
9. allograft rejection: acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin or cornea or following blood transfusion; or chronic graft versus host disease;
10. CNS: Alzheimer's disease and other dementing disorders including CJD and nvCJD; amyloidosis; multiple sclerosis and other demyelinating syndromes; cerebral atherosclerosis and vasculitis; temporal arteritis; myasthenia gravis; acute and chronic pain (acute, intermittent or persistent, whether of central or peripheral origin) including visceral pain, headache, migraine, trigeminal neuralgia, atypical facial pain, joint and bone pain, pain arising from cancer and tumor invasion, neuropathic pain syndromes including diabetic, post-herpetic, and HIV-associated neuropathies; neurosarcoïdosis; central and peripheral nervous system complications of malignant, infectious or autoimmune processes;
- 15 11. other auto-immune and allergic disorders including Hashimoto's thyroiditis, Graves' disease, Addison's disease, diabetes mellitus, idiopathic thrombocytopaenic purpura, eosinophilic fasciitis, hyper-IgE syndrome, antiphospholipid syndrome;
- 20 12. other disorders with an inflammatory or immunological component; including acquired immune deficiency syndrome (AIDS), leprosy, Sezary syndrome, and paraneoplastic syndromes;
- 25 13. cardiovascular: atherosclerosis, affecting the coronary and peripheral circulation; pericarditis; myocarditis , inflammatory and auto-immune cardiomyopathies including myocardial sarcoid; ischaemic reperfusion injuries; endocarditis, valvulitis, and aortitis including infective (for example syphilitic); vasculitides; disorders of the proximal and peripheral veins including phlebitis and thrombosis, including deep vein thrombosis and complications of varicose veins;
- 30 14. oncology: treatment of common cancers including prostate, breast, lung, ovarian, pancreatic, bowel and colon, stomach, skin and brain tumors and malignancies affecting

the bone marrow (including the leukaemias) and lymphoproliferative systems, such as Hodgkin's and non-Hodgkin's lymphoma; including the prevention and treatment of metastatic disease and tumour recurrences, and paraneoplastic syndromes; or,

15. gastrointestinal tract: Coeliac disease, proctitis, eosinophilic gastro-enteritis,

5 mastocytosis, Crohn's disease, ulcerative colitis, microscopic colitis, indeterminant colitis, irritable bowel disorder, irritable bowel syndrome, non-inflammatory diarrhea, food-related allergies which have effects remote from the gut, e.g., migraine, rhinitis and eczema;

in a mammal (for example man).

10 In a further aspect the invention provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, for use in the treatment of asthma {such as bronchial, allergic, intrinsic, extrinsic or dust asthma, particularly chronic or inveterate asthma (for example late asthma or airways hyper-responsiveness)}; or rhinitis {including acute, allergic, atrophic or chronic rhinitis, such as rhinitis caseosa, hypertrophic rhinitis, 15 rhinitis purulenta, rhinitis sicca or rhinitis medicamentosa; membranous rhinitis including croupous, fibrinous or pseudomembranous rhinitis or scrofulous rhinitis; seasonal rhinitis including rhinitis nervosa (hay fever) or vasomotor rhinitis}.

In a still further aspect a compound of formula (I), or a pharmaceutically acceptable salt thereof, is useful in the treatment of asthma.

20 The present invention also provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of asthma {such as bronchial, allergic, intrinsic, extrinsic or dust asthma, particularly chronic or inveterate asthma (for example late asthma or airways hyper-responsiveness)}; or rhinitis {including acute, allergic, atrophic or chronic rhinitis, such as 25 rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca or rhinitis medicamentosa; membranous rhinitis including croupous, fibrinous or pseudomembranous rhinitis or scrofulous rhinitis; seasonal rhinitis including rhinitis nervosa (hay fever) or vasomotor rhinitis}.

The present invention also provides the use of a compound of formula (I), or a 30 pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of an infection due to respiratory syncytial virus.

In order to use a compound of the invention, or a pharmaceutically acceptable salt thereof, for the therapeutic treatment of a mammal, such as man, said ingredient is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition. Therefore in another aspect the present invention provides a 5 pharmaceutical composition which comprises a compound of the formula (I), or a pharmaceutically acceptable salt thereof (active ingredient), and a pharmaceutically acceptable adjuvant, diluent or carrier.

In a further aspect the present invention provides a process for the preparation of said composition which comprises mixing active ingredient with a pharmaceutically acceptable 10 adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical composition will, for example, comprise from 0.05 to 99 %w (per cent by weight), such as from 0.05 to 80 %w, for example from 0.10 to 70 %w, such as from 0.10 to 50 %w, of active ingredient, all percentages by weight being based on total composition.

The pharmaceutical compositions of this invention may be administered in standard 15 manner for the disease condition that it is desired to treat, for example by topical (such as to the lung and/or airways or to the skin), oral, rectal or parenteral administration. For these purposes the compounds of this invention may be formulated by means known in the art. A suitable pharmaceutical composition of this invention is one suitable for oral administration in unit dosage form, for example a tablet or capsule which contains between 20 0.1mg and 1g of active ingredient.

Each patient may receive, for example, a dose of 0.01mgkg^{-1} to 100mgkg^{-1} , for example in the range of 0.1mgkg^{-1} to 20mgkg^{-1} , of the active ingredient administered, for example, 1 to 4 times per day.

The invention further relates to a combination therapy wherein a compound of the 25 invention, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition or formulation comprising a compound of the invention, is administered concurrently or sequentially or as a combined preparation with another therapeutic agent or agents, for the treatment of one or more of the conditions listed.

In particular, for the treatment of the inflammatory diseases such as (but not 30 restricted to) rheumatoid arthritis, osteoarthritis, asthma, allergic rhinitis, chronic obstructive pulmonary disease (COPD), psoriasis, and inflammatory bowel disease, the compounds of the invention may be combined with agents listed below.

Non-steroidal anti-inflammatory agents (hereinafter NSAIDs) including non-selective cyclo-oxygenase COX-1 / COX-2 inhibitors whether applied topically or systemically (such as piroxicam, diclofenac, propionic acids such as naproxen, flurbiprofen, fenoprofen, ketoprofen and ibuprofen, fenamates such as mefenamic acid, 5 indomethacin, sulindac, azapropazone, pyrazolones such as phenylbutazone, salicylates such as aspirin); selective COX-2 inhibitors (such as meloxicam, celecoxib, rofecoxib, valdecoxib, lumarocoxib, parecoxib and etoricoxib); cyclo-oxygenase inhibiting nitric oxide donors (CINODs); glucocorticosteroids (whether administered by topical, oral, intramuscular, intravenous, or intra-articular routes); methotrexate; leflunomide; 10 hydroxychloroquine; d-penicillamine; auranofin or other parenteral or oral gold preparations; analgesics; diacerein; intra-articular therapies such as hyaluronic acid derivatives; and nutritional supplements such as glucosamine.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, together with a cytokine or agonist 15 or antagonist of cytokine function, (including agents which act on cytokine signalling pathways such as modulators of the SOCS system) including alpha-, beta-, and gamma-interferons; insulin-like growth factor type I (IGF-1); interleukins (IL) including IL1 to 17, and interleukin antagonists or inhibitors such as anakinra; tumour necrosis factor alpha (TNF- α) inhibitors such as anti-TNF monoclonal antibodies (for example infliximab; 20 adalimumab, and CDP-870) and TNF receptor antagonists including immunoglobulin molecules (such as etanercept) and low-molecular-weight agents such as pentoxyfylline.

In addition the invention relates to a combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, with a monoclonal antibody targeting B-Lymphocytes (such as CD20 (rituximab), MRA-aIL16R and T-Lymphocytes, CTLA4-Ig, 25 HuMax II-15).

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, with a modulator of chemokine receptor function such as an antagonist of CCR1, CCR2, CCR2A, CCR2B, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10 and CCR11 (for the C-C family); CXCR1, 30 CXCR2, CXCR3, CXCR4 and CXCR5 (for the C-X-C family) and CX₃CR1 for the C-X₃-C family.

The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, with an inhibitor of matrix metalloprotease (MMPs), i.e., the stromelysins, the collagenases, and the gelatinases, as well as aggrecanase; for example collagenase-1 (MMP-1), collagenase-2 (MMP-8),
5 collagenase-3 (MMP-13), stromelysin-1 (MMP-3), stromelysin-2 (MMP-10), and stromelysin-3 (MMP-11) and MMP-9 and MMP-12, including agents such as doxycycline.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and a leukotriene biosynthesis inhibitor, 5-lipoxygenase (5-LO) inhibitor or 5-lipoxygenase activating protein (FLAP)
10 antagonist such as; zileuton; ABT-761; fenleuton; tepoxalin; Abbott-79175; Abbott-85761; a N-(5-substituted)-thiophene-2-alkylsulfonamide; 2,6-di-tert-butylphenolhydrazones; a methoxytetrahydropyrans such as Zeneca ZD-2138; the compound SB-210661; a pyridinyl-substituted 2-cyanonaphthalene compound such as L-739,010; a 2-cyanoquinoline compound such as L-746,530; or an indole or quinoline compound such as
15 MK-591, MK-886, and BAY x 1005.

The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and a receptor antagonist for leukotrienes (LT) B4, LTC4, LTD4, and LTE4. selected from the group consisting of the phenothiazin-3-yls such as L-651,392; amidino compounds such as CGS-25019c;
20 benzoxalamines such as ontazolast; benzenecarboximidamides such as BIIL 284/260; and compounds such as zafirlukast, ablukast, montelukast, pranlukast, verlukast (MK-679), RG-12525, Ro-245913, iralukast (CGP 45715A), and BAY x 7195.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and a phosphodiesterase (PDE)
25 inhibitor such as a methylxanthanine including theophylline and aminophylline; a selective PDE isoenzyme inhibitor including a PDE4 inhibitor an inhibitor of the isoform PDE4D, or an inhibitor of PDE5.

The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and a histamine type 1 receptor
30 antagonist such as cetirizine, loratadine, desloratadine, fexofenadine, acrivastine, terfenadine, astemizole, azelastine, levocabastine, chlorpheniramine, promethazine, cyclizine, or mizolastine; applied orally, topically or parenterally.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and a proton pump inhibitor (such as omeprazole) or a gastroprotective histamine type 2 receptor antagonist.

5 The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and an antagonist of the histamine type 4 receptor.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and an alpha-1/alpha-2 adrenoceptor agonist vasoconstrictor sympathomimetic agent, such as propylhexedrine,
10 phenylephrine, phenylpropanolamine, ephedrine, pseudoephedrine, naphazoline hydrochloride, oxymetazoline hydrochloride, tetrahydrozoline hydrochloride, xylometazoline hydrochloride, tramazoline hydrochloride or ethylnorepinephrine hydrochloride.
15

The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and an anticholinergic agent including muscarinic receptor (M1, M2, and M3) antagonist such as atropine, hyoscine, glycopyrrrolate, ipratropium bromide, tiotropium bromide, oxitropium bromide, pirenzepine or telenzepine.
20

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and a beta-adrenoceptor agonist (including beta receptor subtypes 1-4) such as isoprenaline, salbutamol, formoterol, salmeterol, terbutaline, orciprenaline, bitolterol mesylate, or pirbuterol, or a chiral enantiomer thereof.
25

The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and a chromone, such as sodium cromoglycate or nedocromil sodium.
30

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, with a glucocorticoid, such as flunisolide, triamcinolone acetonide, beclomethasone dipropionate, budesonide, fluticasone propionate, ciclesonide or mometasone furoate.

The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, with an agent that modulates a nuclear hormone receptor such as PPARs.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, together with an immunoglobulin (Ig) or Ig preparation or an antagonist or antibody modulating Ig function such as anti-IgE (for example omalizumab).

The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and another systemic or topically-applied anti-inflammatory agent, such as thalidomide or a derivative thereof, a retinoid, dithranol or calcipotriol.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and combinations of aminosalicylates and sulfapyridine such as sulfasalazine, mesalazine, balsalazide, and olsalazine; and immunomodulatory agents such as the thiopurines, and corticosteroids such as budesonide.

The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, together with an antibacterial agent such as a penicillin derivative, a tetracycline, a macrolide, a beta-lactam, a fluoroquinolone, metronidazole, an inhaled aminoglycoside; an antiviral agent including acyclovir, famciclovir, valaciclovir, ganciclovir, cidofovir, amantadine, rimantadine, ribavirin, zanamavir and oseltamavir; a protease inhibitor such as indinavir, nelfinavir, ritonavir, and saquinavir; a nucleoside reverse transcriptase inhibitor such as didanosine, lamivudine, stavudine, zalcitabine or zidovudine; or a non-nucleoside reverse transcriptase inhibitor such as nevirapine or efavirenz.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and a cardiovascular agent such as a calcium channel blocker, a beta-adrenoceptor blocker, an angiotensin-converting enzyme (ACE) inhibitor, an angiotensin-2 receptor antagonist; a lipid lowering agent such as a statin or a fibrate; a modulator of blood cell morphology such as pentoxyfylline; a thrombolytic, or an anticoagulant such as a platelet aggregation inhibitor.

The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and a CNS agent such as an antidepressant (such as sertraline), an anti-Parkinsonian drug (such as deprenyl, L-dopa, ropinirole, pramipexole, a MAOB inhibitor such as selegiline and rasagiline, a comP 5 inhibitor such as tasmar, an A-2 inhibitor, a dopamine reuptake inhibitor, an NMDA antagonist, a nicotine agonist, a dopamine agonist or an inhibitor of neuronal nitric oxide synthase), or an anti-Alzheimer's drug such as donepezil, rivastigmine, tacrine, a COX-2 inhibitor, propentofylline or metrifonate.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and an agent for the treatment of acute or chronic pain, such as a centrally or peripherally-acting analgesic (for example an opioid or derivative thereof), carbamazepine, phenytoin, sodium valproate, amitryptiline or other anti-depressant agents, paracetamol, or a non-steroidal anti-inflammatory agent.

The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, together with a parenterally or topically-applied (including inhaled) local anaesthetic agent such as lignocaine or a derivative thereof.

A compound of the present invention, or a pharmaceutically acceptable salt thereof, can also be used in combination with an anti-osteoporosis agent including a hormonal agent such as raloxifene, or a biphosphonate such as alendronate.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, together with a: (i) tryptase inhibitor; (ii) platelet activating factor (PAF) antagonist; (iii) interleukin converting enzyme (ICE) inhibitor; (iv) IMPDH inhibitor; (v) adhesion molecule inhibitors including 25 VLA-4 antagonist; (vi) cathepsin; (vii) kinase inhibitor such as an inhibitor of tyrosine kinase (such as Btk, Itk, Jak3 or MAP, for example Gefitinib or Imatinib mesylate), a serine / threonine kinase (such as an inhibitor of a MAP kinase such as p38, JNK, protein kinase A, B or C, or IKK), or a kinase involved in cell cycle regulation (such as a cyclin dependent kinase); (viii) glucose-6 phosphate dehydrogenase inhibitor; (ix) kinin-B.sub1. - 30 or B.sub2. -receptor antagonist; (x) anti-gout agent, for example colchicine; (xi) xanthine oxidase inhibitor, for example allopurinol; (xii) uricosuric agent, for example probenecid, sulfinpyrazone or benz bromarone; (xiii) growth hormone secretagogue; (xiv) transforming

growth factor (TGF β); (xv) platelet-derived growth factor (PDGF); (xvi) fibroblast growth factor for example basic fibroblast growth factor (bFGF); (xvii) granulocyte macrophage colony stimulating factor (GM-CSF); (xviii) capsaicin cream; (xix) tachykinin NK.sub1. or NK.sub3. receptor antagonist such as NKP-608C, SB-233412 (talnetant) or D-4418; (xx) elastase inhibitor such as UT-77 or ZD-0892; (xxi) TNF-alpha converting enzyme inhibitor (TACE); (xxii) induced nitric oxide synthase (iNOS) inhibitor; (xxiii) chemoattractant receptor-homologous molecule expressed on TH2 cells, (such as a CRTH2 antagonist); (xxiv) inhibitor of p38; (xxv) agent modulating the function of Toll-like receptors (TLR), (xxvi) agent modulating the activity of purinergic receptors such as P2X7; (xxvii) inhibitor of transcription factor activation such as NFkB, API, or STATS; or (xxviii) a non-steroidal glucocorticoid receptor agonist.

A compound of the invention, or a pharmaceutically acceptable salt thereof, can also be used in combination with an existing therapeutic agent for the treatment of cancer, for example suitable agents include:

- (i) an antiproliferative/antineoplastic drug or a combination thereof, as used in medical oncology, such as an alkylating agent (for example cis-platin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan or a nitrosourea); an antimetabolite (for example an antifolate such as a fluoropyrimidine like 5-fluorouracil or tegafur, raltitrexed, methotrexate, cytosine arabinoside, hydroxyurea, gemcitabine or paclitaxel); an antitumour antibiotic (for example an anthracycline such as adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin or mithramycin); an antimitotic agent (for example a vinca alkaloid such as vincristine, vinblastine, vindesine or vinorelbine, or a taxoid such as taxol or taxotere); or a topoisomerase inhibitor (for example an epipodophyllotoxin such as etoposide, teniposide, amsacrine, topotecan or a camptothecin);
- (ii) a cytostatic agent such as an antioestrogen (for example tamoxifen, toremifene, raloxifene, droloxifene or iodoxyfene), an oestrogen receptor down regulator (for example fulvestrant), an antiandrogen (for example bicalutamide, flutamide, nilutamide or cyproterone acetate), a LHRH antagonist or LHRH agonist (for example goserelin, leuprorelin or buserelin), a progestogen (for example megestrol acetate), an aromatase inhibitor (for example as anastrozole, letrozole, vorazole or exemestane) or an inhibitor of 5 α -reductase such as finasteride;

(iii) an agent which inhibits cancer cell invasion (for example a metalloproteinase inhibitor like marimastat or an inhibitor of urokinase plasminogen activator receptor function);

(iv) an inhibitor of growth factor function, for example: a growth factor antibody (for example the anti-erb b2 antibody trastuzumab, or the anti-erb b1 antibody cetuximab [C225]), a farnesyl transferase inhibitor, a tyrosine kinase inhibitor or a serine/threonine kinase inhibitor, an inhibitor of the epidermal growth factor family (for example an EGFR family tyrosine kinase inhibitor such as N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (gefitinib, AZD1839), N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI-774) or 6-acrylamido-N-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)quinazolin-4-amine (CI 1033)), an inhibitor of the platelet-derived growth factor family, or an inhibitor of the hepatocyte growth factor family;

(v) an antiangiogenic agent such as one which inhibits the effects of vascular endothelial growth factor (for example the anti-vascular endothelial cell growth factor antibody bevacizumab, a compound disclosed in WO 97/22596, WO 97/30035, WO 97/32856 or WO 98/13354), or a compound that works by another mechanism (for example linomide, an inhibitor of integrin $\alpha v\beta 3$ function or an angiostatin);

(vi) a vascular damaging agent such as combretastatin A4, or a compound disclosed in WO 99/02166, WO 00/40529, WO 00/41669, WO 01/92224, WO 02/04434 or WO 02/08213;

(vii) an agent used in antisense therapy, for example one directed to one of the targets listed above, such as ISIS 2503, an anti-ras antisense;

(viii) an agent used in a gene therapy approach, for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene-directed enzyme pro-drug therapy) approaches such as those using cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or radiotherapy such as multi-drug resistance gene therapy; or,

(ix) an agent used in an immunotherapeutic approach, for example ex-vivo and in-vivo approaches to increase the immunogenicity of patient tumour cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, approaches to decrease T-cell anergy, approaches using transfected immune cells such as cytokine-transfected dendritic cells, approaches using cytokine-transfected tumour cell lines and approaches using anti-idiotypic antibodies.

The invention will now be illustrated by the following non-limiting examples in which, unless stated otherwise:

(i) when given, ^1H NMR data is quoted and is in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard, determined at 300MHz or 400MHz using perdeuterio DMSO-D6 (CD_3SOCD_3) or CDCl_3 as the solvent unless otherwise stated;

(ii) mass spectra (MS) were run with an electron energy of 70 electron volts in the chemical ionisation (CI) mode using a direct exposure probe; where indicated ionisation was effected by electron impact (EI) or fast atom bombardment (FAB); where values for m/z are given, generally only ions which indicate the parent mass are reported, and unless otherwise stated the mass ion quoted is the positive mass ion - $(\text{M}+\text{H})^+$;

(iii) the title and sub-title compounds of the examples and methods were named using the index name program from Advanced Chemistry Development Inc, version 6.00, or with the AUTONOM program available from Beilstein informations systeme GmbH;

(iv) unless stated otherwise, reverse phase HPLC was conducted using a "Symmetry", "NovaPak" or "Xterra" reverse phase silica column, all available from Waters Corp.;

(v) for analytical HPLC the following conditions were used:

Reverse phase analytical HPLC (Hewlett Packard Series 1100) using Waters "Symmetry" C8 column 3.5 μm ; 4.6 x 50mm column using 0.1% ammonium acetate/acetonitrile

gradients at 2 mL/min given as % aqueous

STANDARD 75% to 5% over 3 min

FAST 45% to 5% over 2.5 min

MEDIUM FAST 65% to 5% in 2.5 min

SLOW 95% to 50% in 2.5 min

25 SUPERSLOW 100% to 80% in 2.5 min; and

(vi) the following abbreviations are used:

RPHPLC	Reverse phase high pressure liquid chromatography
min	minutes
h	hour

EXAMPLE 1

This Example illustrates the preparation of methyl (2*S*)-3-cyclohexyl-2-(4-{[4-(3,4-dichlorophenoxy)piperidin-1-yl]methyl}piperidin-1-yl)propanoate

4-[[4-(3,4-Dichlorophenoxy)-1-piperidinyl]methyl]-1,2-cyclopentanediol

(WO200487659; 380 mg) was dissolved in water (5 mL) containing 1 drop acetic acid. Sodium periodate (229 mg) was added and the mixture was stirred for 1 h. Potassium carbonate (190 mg) was added and the mixture was extracted with dichloromethane (2 x 10 mL). The organic phases were dried and filtered and the resulting solution was added to a solution of methyl 3-cyclohexyl-L-alaninate hydrochloride (234 mg), sodium triacetoxyborohydride (513 mg), triethylamine (0.16 mL) and acetic acid (0.1 mL) in dichloromethane (10 mL). The mixture was stirred for 2.5 h and was then poured into aqueous sodium bicarbonate solution. The mixture was extracted with ethyl acetate; the organic phase was dried, filtered and evaporated. The residue was purified by chromatography (silica, eluent ethyl acetate) to give the title compound (253 mg).

MS [M+H]⁺ (ES+) 511/513; Retention time 2.99 fast gradient.

The following compounds were prepared analogously from the appropriate esters and diols:

Example	Name	MS [M+H] ⁺ (ES+)	Retention time gradient
2	Methyl (2 <i>S</i>)-3-cyclohexyl-2-(4-{[4-(3,4-dichloro-2-methylphenoxy)piperidin-1-yl]methyl}piperidin-1-yl)propanoate		3.6 (fast)
3	Methyl (2 <i>S</i>)-3-cyclopropyl-2-(4-{[4-(3,4-dichloro-2-methylphenoxy)piperidin-1-yl]methyl}piperidin-1-yl)propanoate	483/485	2.19 (fast)
4	Methyl (2 <i>S</i>)-3-cyclopentyl-2-(4-{[4-(3,4-dichlorophenoxy)piperidin-1-yl]methyl}piperidin-1-yl)propanoate	497/499	2.70 (fast)

5	Methyl (2S)-3-cyclopentyl-2-(4-{[4-(3,4-dichloro-2-methylphenoxy)piperidin-1-yl]methyl}piperidin-1-yl)propanoate	511/513	3.04 (fast)
6	Methyl 1-(4-{[4-(3,4-dichlorophenoxy)piperidin-1-yl]methyl}piperidin-1-yl)cyclohexanecarboxylate	483/485	2.61 (fast)
7	Methyl 1-(4-{[4-(3,4-dichloro-2-methylphenoxy)piperidin-1-yl]methyl}piperidin-1-yl)cyclohexanecarboxylate	497/499	2.19 (fast)
8	Methyl 1-(4-{[4-(3,4-dichloro-2-methylphenoxy)piperidin-1-yl]methyl}piperidin-1-yl)cyclopentanecarboxylate	483/485	2.19 (fast)
9	Methyl (2S)-2-{4-[4-(3,4-Dichloro-2-methyl-phenoxy)-piperidin-1-ylmethyl]-piperidin-1-yl}-4-methyl-pentanoate	485/487	2.57 (fast)
10	Methyl (2S)-2-{4-[4-(3,4-Dichloro-phenoxy)-piperidin-1-ylmethyl]-piperidin-1-yl}-4-methyl-pentanoate	471/473	2.39 (fast)
11	Methyl (2S)-2-{4-[4-(4-Chloro-2-methyl-phenoxy)-piperidin-1-ylmethyl]-piperidin-1-yl}-3-methyl-butyrate		
12	<i>tert</i> -Butyl 1-(4-{[4-(4-fluoro-2-methylphenoxy)piperidin-1-yl]methyl}piperidin-1-yl)cyclohexanecarboxylate	489	2.86 (fast)
13	<i>tert</i> -Butyl 1-(4-{[4-(4-chloro-2-methylphenoxy)piperidin-1-yl]methyl}piperidin-1-yl)cyclohexanecarboxylate	505/507	3.45 (fast)
14	Methyl (2S)-2-(4-{[4-(3,4-dichlorophenoxy)piperidin-1-yl]methyl}piperidin-1-yl)-3-methylbutanoate	457/459	

15	Methyl (2S) 2-{4-[4-(3,4-dichloro-2-methyl-phenoxy)-piperidin-1-ylmethyl]-piperidin-1-yl}-2,4-dimethyl-pentanoate	499/501	3.20 (fast)
16	Methyl (2S) 2-{4-[4-(4-chloro-2-methyl-phenoxy)-piperidin-1-ylmethyl]-piperidin-1-yl}-2,4-dimethyl-pentanoate		2.52 (fast)

EXAMPLE 1A

This Example illustrates the preparation of (2S)-3-cyclohexyl-2-(4-{[4-(3,4-

5 dichloro-2-methylphenoxy)piperidin-1-yl]methyl}piperidin-1-yl)propanoic acid

Methyl (2S)-3-cyclohexyl-2-(4-{[4-(3,4-dichlorophenoxy)piperidin-1-
ylyl]methyl}piperidin-1-yl)propanoate (253 mg; Example 1) was dissolved in
tetrahydrofuran (15 mL) and a solution of lithium hydroxide (170 mg) in water (10 mL)
was added. The mixture was stirred overnight and then the volatiles were evaporated. The
10 residue was acidified with acetic acid and purified by RPHPLC (gradient 75:25 → 5:95
0.1% aq ammonium acetate : acetonitrile with loading via a 7.5% acetonitrile at-column
dilution stream) to give the title compound (28 mg).

15 ^1H NMR $\delta_{(\text{CD}_3\text{OD}+\text{NaOD})}$ 0.81 - 1.07 (4H, m), 1.11 - 1.42 (8H, m), 1.50 - 1.84 (8H,
m), 1.89 - 2.08 (2H, m), 2.23 (2H, d), 2.28 - 2.40 (4H, m), 2.65 - 2.78 (2H, m), 2.93 - 3.12
(3H, m), 4.34 - 4.46 (1H, m), 6.90 (1H, dd), 7.10 (1H, d), 7.39 (1H, d)
MS (ES-ve) (M-H)- 495/497

The following compounds were prepared from the corresponding ester using the
method of Example 1A:

Example	Name	MS [M+H] ⁺ (APCI+); RT (std)	^1H NMR $\delta_{(\text{CD}_3\text{OD}+\text{NaOD})}$ (unless otherwise indicated)
2A	(2S)-3-Cyclohexyl-2-(4-{[4-(3,4-dichloro-2-methylphenoxy)piperidin-1-	511/513	$\delta_{(\text{D}_2\text{O})}$ 0.85 - 1.43 (7H, m), 1.57 - 1.87 (8H, m), 1.96 - 2.42 (10H, m), 2.97 - 3.37 (6H, m),

	yl]methyl}piperidin-1-yl)propanoic acid		3.51 - 3.79 (5H, m), 4.55 - 4.66 (0.5H, m), 4.82 - 4.86 (0.5H, m), 6.99 (0.5H, d), 7.05 (0.5H, d), 7.40 (1H, d)
3A	(2 <i>S</i>)-3-Cyclopropyl-2-(4-{[4-(3,4-dichloro-2-methylphenoxy)piperidin-1-yl]methyl}piperidin-1-yl)propanoic acid	469/471	-0.03 - 0.03 (1H, m), 0.06 - 0.15 (1H, m), 0.39 (2H, d), 0.63 - 0.76 (1H, m), 1.08 - 1.32 (3H, m), 1.46 - 1.58 (1H, m), 1.66 - 1.83 (5H, m), 1.92 - 2.02 (2H, m), 2.19 (2H, d), 2.21 - 2.37 (4H, m), 2.27 (3H, s), 2.57 - 2.69 (2H, m), 2.90 - 3.01 (3H, m), 4.35 - 4.43 (1H, m), 6.88 (1H, d), 7.24 (1H, d)
4A	(2 <i>S</i>)-3-Cyclopentyl-2-(4-{[4-(3,4-dichlorophenoxy)piperidin-1-yl]methyl}piperidin-1-yl)propanoic acid	483/485	1.06 - 1.20 (2H, m), 1.22 - 1.34 (1H, m), 1.38 - 1.46 (1H, m), 1.47 - 1.66 (5H, m), 1.69 - 1.84 (7H, m), 1.84 - 1.94 (2H, m), 1.95 - 2.03 (2H, m), 2.21 (2H, d), 2.23 - 2.37 (4H, m), 2.64 - 2.74 (2H, m), 2.93 - 3.02 (3H, m), 4.33 - 4.41 (1H, m), 6.87 (1H, dd), 7.07 (1H, d), 7.36 (1H, d)
5A	3-Cyclopentyl-2-{4-[4-(3,4-dichloro-2-methyl-phenoxy)-piperidin-1-ylmethyl]-piperidin-1-yl}-propionic acid	497/499	1.06 - 1.20 (3H, m), 1.21 - 1.35 (1H, m), 1.38 - 1.66 (6H, m), 1.70 - 1.84 (6H, m), 1.85 - 1.94 (2H, m), 1.95 - 2.03 (2H, m), 2.21 (2H, d), 2.24 - 2.38 (4H, m), 2.30 (3H, s), 2.60 - 2.72 (2H, m), 2.93 - 3.02 (3H,

			m), 4.36 - 4.46 (1H, m), 6.90 (1H, d), 7.27 (1H, d)
6A	1-(4-{[4-(3,4-dichlorophenoxy)piperidin-1-yl]methyl}piperidin-1-yl)cyclohexanecarboxylic acid	469/471 1.48	1.12 - 1.32 (4H, m), 1.35 - 1.44 (2H, m), 1.48 - 1.56 (2H, m), 1.60 - 1.68 (2H, m), 1.69 - 1.79 (4H, m), 1.94 - 2.02 (2H, m), 2.15 - 2.32 (7H, m), 2.64 - 2.74 (2H, m), 3.09 - 3.16 (2H, m), 4.32 - 4.41 (1H, m), 6.87 (1H, dd), 7.08 (1H, d), 7.36 (1H, d)
7A	1-(4-{[4-(3,4-dichloro-2-methylphenoxy)piperidin-1-yl]methyl}piperidin-1-yl)cyclohexanecarboxylic acid	483/485 0.77 (fast)	1.13 - 1.32 (5H, m), 1.35 - 1.44 (2H, m), 1.48 - 1.56 (2H, m), 1.61 - 1.69 (2H, m), 1.70 - 1.84 (4H, m), 1.94 - 2.03 (2H, m), 2.15 - 2.37 (8H, m), 2.30 (3H, s), 2.62 - 2.70 (2H, m), 3.09 - 3.16 (2H, m), 4.37 - 4.44 (1H, m), 6.90 (1H, d), 7.26 (1H, d)
8A	1-(4-{[4-(3,4-dichloro-2-methylphenoxy)piperidin-1-yl]methyl}piperidin-1-yl)cyclopentanecarboxylic acid	469/471 0.72 (fast)	1.17 - 1.29 (2H, m), 1.41 - 1.84 (11H, m), 1.94 - 2.04 (2H, m), 2.21 (2H, d), 2.31 (3H, s), 2.32 - 2.42 (6H, m), 2.61 - 2.71 (2H, m), 2.94 - 3.01 (2H, m), 4.37 - 4.45 (1H, m), 6.90 (1H, d), 7.26 (1H, d)
9A	(2S)-2-{4-[4-(3,4-Dichloro-2-methyl-phenoxy)-piperidin-1-ylmethyl]-piperidin-1-yl}-4-methyl-pentanoic acid	469/471 (APCI-)	0.92 (3H, d), 0.94 (3H, d), 1.11 - 1.22 (1H, m), 1.22 - 1.35 (2H, m), 1.49 - 1.66 (2H, m), 1.70 - 1.84 (5H, m), 1.94 -

			2.03 (2H, m), 2.21 (2H, d), 2.24 - 2.37 (4H, m), 2.30 (3H, s), 2.61 - 2.70 (2H, m), 2.94 - 3.03 (3H, m), 4.37 - 4.45 (1H, m), 6.90 (1H, d), 7.25 (1H, d)
10A	2-{4-[4-(3,4-Dichloro-phenoxy)-piperidin-1-ylmethyl]-piperidin-1-yl}-4-methyl-pentanoic acid	457/459	0.93 (6H, t), 1.09 - 1.20 (1H, m), 1.29 (2H, t), 1.49 - 1.67 (2H, m), 1.69 - 1.81 (5H, m), 1.93 - 2.02 (2H, m), 2.20 (2H, d), 2.24 - 2.40 (4H, m), 2.64 - 2.74 (2H, m), 2.95 (2H, d), 3.00 - 3.06 (1H, m), 4.31 - 4.41 (1H, m), 6.85 - 6.89 (1H, m), 7.07 (1H, d), 7.36 (1H, d)
11A	2-{4-[4-(4-Chloro-2-methyl-phenoxy)-piperidin-1-ylmethyl]-piperidin-1-yl}-3-methyl-butyrinic acid	423/425	1.01 (3H, d), 1.13 (3H, d), 1.41 - 1.60 (2H, m), 1.75 - 1.91 (4H, m), 1.93 - 2.04 (6H, m), 2.16 (3H, s), 2.31 (2H, d), 2.36 - 2.44 (1H, m), 2.68 - 2.76 (2H, m), 2.93 - 3.05 (2H, m), 3.45 - 3.56 (2H, m), 4.35 - 4.42 (1H, m), 6.86 (1H, d), 7.06 (1H, d), 7.09 (1H, d)

Example 12A

1-{4-[4-(4-Fluoro-2-methyl-phenoxy)-piperidin-1-ylmethyl]-piperidin-1-yl}-cyclohexanecarboxylic acid dihydrochloride

5 tert-Butyl 1-{4-[4-(4-fluoro-2-methyl-phenoxy)-piperidin-1-ylmethyl]-piperidin-1-yl}-cyclohexanecarboxylate (0.2 g) was stirred and sonicated in aq. HCl (20 mL, 6M) for 16h. The solvents were evaporated and the residue was redissolved in aqueous ammonium acetate solution; acetonitrile was added. The layers were separated and the organic layer

was evaporated, a solid formed which was filtered, washed with water and ether. The solid was taken up in 6M aq. HCl and evaporated to give the title compound (64mg).

¹H NMR δ_(CD₃OD+NaOD) 1.11 - 1.83 (15H, m), 1.92 - 2.01 (2H, m), 2.13 - 2.35 (11H, m), 2.63 - 2.71 (2H, m), 3.08 - 3.16 (2H, m), 4.25 - 4.34 (1H, m), 6.75 - 6.90 (3H, m)

5 MS [M+H]⁺ 433 (ES+)

RT 1.23 (standard)

Example 13A

10 1-(4-{[4-(4-Chloro-2-methylphenoxy)piperidin-1-yl]methyl}piperidin-1-yl)cyclohexanecarboxylic acid dihydrochloride

tert-Butyl 1-{4-[4-(4-chloro-2-methyl-phenoxy)-piperidin-1-ylmethyl]-piperidin-1-yl}-cyclohexanecarboxylate (0.18 g) was stirred in 6 M HCl (10 mL) for 16h. Additional HCl (conc, 3 mL) was added and the mixture was stirred for a further 3 h. The volume of solvent was reduced and product precipitated to give the title compound (24 mg).

15 ¹H NMR δ_(CD₃OD+NaOD) 1.18 - 1.35 (1H, m), 1.42 - 1.59 (2H, m), 1.66 - 1.79 (5H, m), 1.81 - 1.95 (2H, m), 1.95 - 2.12 (1H, m), 2.14 - 2.37 (10H, m), 2.41 - 2.50 (2H, m), 3.10 - 3.22 (6H, m), 3.50 - 3.58 (1H, m), 3.65 - 3.78 (3H, m), 6.90 - 6.99 (1H, m), 7.10 - 7.20 (2H, m)

MS [M+H]⁺ 449/451 (APCI+)

20 RT 1.70 (std)

Example 14A

25 (2S)-2-(4-{[4-(3,4-Dichlorophenoxy)piperidin-1-yl]methyl}piperidin-1-yl)-3-methylbutanoic acid

Methyl (2S)-2-(4-{[4-(3,4-dichlorophenoxy)piperidin-1-yl]methyl}piperidin-1-yl)-3-methylbutanoate (35 mg) was taken up in aq. HCl (6 M, 40 mL)) and the reaction mixture was heated to 80 °C for 48 h. The solvents were evaporated, the residue was taken up in methanol and purified via RP-prep-HPLC (gradient 0.1% aqueous ammonium acetate : acetonitrile 95:5 to 50:50 over 25 min) to give title compound (22 mg).

30 ¹H NMR δ_(CD₃OD+NaOD) 1.02 (3H, d), 1.14 (3H, d), 1.26 - 1.38 (3H, m), 1.42 - 1.64 (2H, m), 1.73 - 1.85 (2H, m), 1.98 - 2.07 (4H, m), 2.28 - 2.39 (2H, m), 2.40 - 2.49 (2H, m),

2.75 - 2.84 (2H, m), 2.97 - 3.04 (2H, m), 3.46 - 3.58 (2H, m), 4.39 - 4.46 (1H, m), 6.89 (1H, dd), 7.10 (1H, d), 7.38 (1H, d)

MS [M+H]⁺ 443/445 (APCI+)

RT 1.58 (std)

5

Example 15A

(2S)-2-{4-[4-(3,4-Dichloro-2-methyl-phenoxy)-piperidin-1-ylmethyl]-piperidin-1-yl}-2,4-dimethyl-pentanoic acid

A mixture of methyl (2S)-2-{4-[4-(3,4-Dichloro-2-methyl-phenoxy)-piperidin-1-ylmethyl]-piperidin-1-yl}-2,4-dimethyl-pentanoate (50 mg), barium hydroxide (82 mg), NMP (2 mL), water (1 mL) and methanol (1 mL) were heated together in a microwave at 190 °C for 3 h. The mixture was then acidified with acetic acid (1 mL), filtered, and purified by reverse-phase hplc (95:5 0.1% aqueous ammonium acetate/acetonitrile to 5:95 0.1% aqueous ammonium acetate/acetonitrile over 10 minutes, symmetry column)to give the title compound (33 mg).

¹H NMR δ_(CD3OD+NaOD) 0.89 - 0.94 (6H, m), 1.15 - 1.30 (3H, m), 1.17 (3H, s), 1.39 - 1.45 (1H, m), 1.46 - 1.57 (1H, m), 1.64 - 1.84 (5H, m), 1.94 - 2.03 (2H, m), 2.08 (2H, t), 2.21 (2H, d), 2.27 - 2.37 (2H, m), 2.30 (3H, s), 2.61 - 2.71 (2H, m), 2.95 (1H, d), 3.04 (1H, d), 4.36 - 4.45 (1H, m), 6.90 (1H, d), 7.26 (1H, d)

MS [M+H]⁺ 485/487 (APCI+)

The following compound was prepared by the method of Example 15A :

Example	Name	MS [M+H] ⁺ (APCI+); RT (std)	¹ H NMR
16A	(2S)-2-{4-[4-(4-Chloro-2-methyl-phenoxy)-piperidin-1-ylmethyl]-piperidin-1-yl}-2,4-dimethyl-pentanoic acid	449/451	0.95 - 1.06 (6H, m), 1.29 - 1.37 (1H, m), 1.39 - 1.48 (3H, m), 1.52 - 1.70 (3H, m), 1.74 - 1.90 (5H, m), 1.95 - 2.13 (4H, m), 2.20 (3H, s), 2.30 (2H, d),

			2.34 - 2.46 (2H, m), 2.66 - 2.79 (2H, m), 2.88 - 3.13 (3H, m), 4.35 - 4.48 (1H, m), 6.90 (1H, d), 7.05 - 7.17 (2H, m)
--	--	--	---

EXAMPLE 17Human eosinophil chemotaxis

Human eosinophils are isolated from EDTA anticoagulated peripheral blood as previously described (Hansel et al., *J. Immunol. Methods*, 1991, 145, 105-110). The cells are resuspended at 10×10^6 mL⁻¹ in RPMI containing 200 IU/ mL penicillin, 200 µg/ mL streptomycin sulfate and supplemented with 10% HIFCS, at room temperature.

Eosinophils (700 µl) are pre-incubated for 15 mins at 37° C with 7 µl of either vehicle or compound (100x required final concentration in 10% DMSO). A chemotaxis plate (ChemoTx, 3µm pore, Neuroprobe) can be loaded by adding 28µl of a concentration of eotaxin 0.1 to 100nM (a selective CCR3 agonist over this concentration range) containing a concentration of a compound according to the Examples or solvent to the lower wells of the chemotaxis plate. The filter is then placed over the wells and 25 µl of eosinophil suspension is added to the top of the filter. The plate is incubated for 1 hr at 37°C in a humidified incubator with a 95% air/5% CO₂ atmosphere to allow chemotaxis.

The medium, containing cells that had not migrated, is carefully aspirated from above the filter and discarded. The filter is then washed once with phosphate buffered saline (PBS) containing 5 mM EDTA to remove any adherent cells. Cells that have migrated through the filter are pelleted by centrifugation (300xg for 5 mins at room temperature) and the filter removed and the supernatant transferred to each well of a 96-well plate (Costar). The pelleted cells are lysed by the addition of 28 µl of PBS containing 0.5% Triton x100 followed by two cycles of freeze/thawing. The cell lysate is then added to the supernatant. The number of eosinophils migrating can be quantified according to the method of Strath et al., *J. Immunol. Methods*, 1985, 83, 209 by measuring eosinophil peroxidase activity in the supernatant.

EXAMPLE 18

Histamine H1 receptor binding activity of compounds of the invention was assessed by competition displacement of 1nM [³H]-pyrilamine (Amersham, Bucks, Product code TRK 608, specific activity 30Ci/mmol) to 2µg membranes prepared from recombinant CHO-K1 cells expressing the human H1 receptor (Euroscreen SA, Brussels, Belgium, product code ES-390-M) in assay buffer (50mM Tris pH 7.4 containing 2mM MgCl₂, 250mM sucrose and 100mM NaCl) for 1 hour at room temperature.

The following compounds of the invention gave inhibition of [³H] pyrilimine binding:

Example	H1 pKi
1A	7.2
2A	7.1
3A	6.7
4A	6.9
6A	6.3
8A	6.5
13A	6.2

10

EXAMPLE 19Eotaxin-2-induced shape change in eosinophils in human blood *in vitro*

See for example, Differential regulation of eosinophil chemokine signaling via CCR3 and non-CCR3 pathways. Sabroe I, Hartnell A, Jopling LA, Bel S, Ponath PD, Pease JE, Collins PD, Williams TJ. *J Immunol.* 1999 Mar 1;162(5):2946-55.

15

Human blood, collected by venous puncture into 9 mL lithium-heparin tubes, was incubated with the CCR3 agonist eotaxin-2 in the presence of vehicle (0.1% (v/v) DMSO) or test compound for 4 min at 37°C in a deep, 96-square-well plate. The blood was fixed with Optilyse B (100 µL) at room temperature for 10 min and then the red blood cells were lysed with distilled water (1 mL) for 60 min at room temperature.

20

The plate was centrifuged at room temperature for 5 min at 300 g. The pellet was re-suspended in assay buffer (PBS without CaCl₂ and MgCl₂, containing HEPES (10 mM), Glucose (10 mM) and 0.1% (w/v) BSA, pH 7.4)) and the samples were analysed using flow cytometry (FC500, Beckman Coulter). The high autofluorescence of eosinophils allowed them to be identified as a discrete population from the other blood cell types.

Eosinophil shape was monitored as the refractive index of the eosinophil population as determined using the forward scatter signal in flow cytometry.

Eotaxin-2 induced a concentration-dependent change in the forward scatter of eosinophils and these data were used to construct a concentration effect curve (E/[A] curve). The rightward displacement of the eotaxin-2 E/[A] curve in the presence of a CCR3 antagonist was used to estimate a pA₂ value in blood using the following equation:

$$\text{Single pA}_2 = -\log_{10} ([B] / (r-1))$$

where r is the ratio of the concentrations required for half maximal effects of eotaxin-2 in the absence and presence of antagonist ($[A]_{50}$ for eotaxin-2 in the presence of antagonist divided by $[A]_{50}$ for control eotaxin-2 curve) and [B] is the molar concentration of antagonist.

EXAMPLE 20

Determination Of Compound Affinity At Human Recombinant CCR3 Receptors

15 Assessed By Competition Of [³H]-4-(2,4-dichloro-3-methylphenoxy)-1'-[4-(methylsulfonyl)benzoyl]-1,4'-bipiperidine for CHO-K1 Cell Membranes In Vitro

Membranes, prepared from CHO-K1 cells stably expressing recombinant human CCR3, suspended in assay buffer (50 mM Tris-Base, pH 7.4; containing sodium chloride (100mM) and magnesium chloride (2 mM)) were incubated in the presence of 2 nM [³H]-4-(2,4-dichloro-3-methylphenoxy)-1'-(4-(methylsulfonyl)benzoyl)-1,4'-bipiperidine, along 20 with vehicle (1 % (v/v) DMSO), 4-(4-chloro-3-methylphenoxy)-1'-(2-(methylsulfonyl)benzoyl)-1,4'-bipiperidine (to define non-specific binding) or test compound for 2 h at 37 °C in round bottomed 96-well plates. The plates were then filtered onto GF/B filter plates, pre-soaked for 1 hour in plate-coating solution (0.3% (w/v) polyethylenimine, 0.2% (w/v) BSA in de-ionised water), using a 96-well plate Tomtec cell harvester. Four washes (250µL) with wash buffer (50 mM Tris-Base, pH 7.4 containing 25 sodium chloride (500 mM) and magnesium chloride (2 mM)) were performed at 4 °C to remove unbound radioactivity. Plates were dried and MicroScint-O (50 µL) was added to each well. The plates were sealed (TopSeal A) and filter-bound radioactivity was measured with a scintillation counter (TopCount, Packard BioScience) using a 1 minute counting protocol.

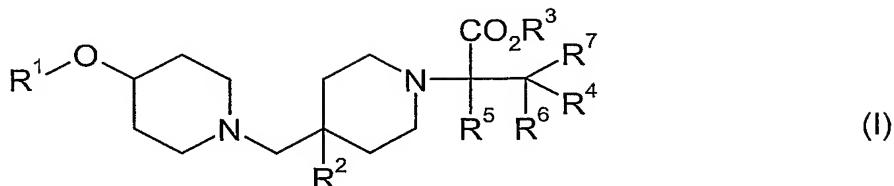
Specific binding was determined from values of the control wells minus the values for the NSB wells for each assay plate. pIC₅₀ values were calculated using a four parameter logistic fit (where pIC₅₀ is defined as the negative logarithm of the concentration of compound required for 50% reduction in specific [³H]- 4-(2,4-dichloro-3-methylphenoxy)-1'-[4-(methylsulfonyl)benzoyl]-1,4'-bipiperidine binding). Data were presented as mean pKi values (calculated by applying a Cheng-Prussoff correction to pIC₅₀ values) from a minimum of 2 separate experiments.

The following compound of the invention gave inhibition of binding :

Example	CCR3 pKi
16A	9.2

CLAIMS

1. A compound of formula (I):



5 wherein:

R¹ is phenyl optionally substituted by halogen, cyano, C₁₋₄ alkyl or C₁₋₄ alkoxy;

R² is hydrogen or hydroxy;

R³ is hydrogen, C₁₋₆ alkyl or phenyl(C₁₋₄ alkyl); wherein phenyl is optionally substituted with halogen, hydroxy, nitro, S(O)_q(C₁₋₄ alkyl), S(O)₂NH₂, S(O)₂NH(C₁₋₄ alkyl), S(O)₂N(C₁₋₄ alkyl)₂, cyano, C₁₋₄ alkyl, C₁₋₄ alkoxy, C(O)NH₂, C(O)NH(C₁₋₄ alkyl), C(O)N(C₁₋₄ alkyl)₂, CO₂H, CO₂(C₁₋₄ alkyl), NHC(O)(C₁₋₄ alkyl), NHS(O)₂(C₁₋₄ alkyl), C(O)(C₁₋₄ alkyl), CF₃ or OCF₃;

10 q is 0, 1 or 2;

R⁴ is methyl, CH(CH₃)₂, or C₃₋₇ cycloalkyl optionally substituted by C₁₋₄ alkyl;

15 R⁵, R⁶ and R⁷ are, independently, hydrogen or methyl;

or R⁴ and R⁵ join to form a 3-7 membered carbocyclic ring optionally substituted by C₁₋₄ alkyl; and two of the ring carbons of this ring can be joined through a 1 or 2 carbon alkylene chain (which is itself optionally substituted by C₁₋₄ alkyl) such that a bicyclic ring system is formed;

20 or a N-oxide thereof; or a pharmaceutically acceptable salt thereof.

2. A compound as claimed in claim 1 wherein R¹ is phenyl optionally substituted with fluorine, chlorine, cyano or C₁₋₄ alkyl.

25 3. A compound as claimed in claim 1 or 2 wherein R² is hydrogen.

4. A compound as claimed in claim 1, 2 or 3 wherein R³ is hydrogen or C₁₋₆ alkyl.

5. A compound as claimed in claim 1, 2, 3 or 4 wherein R³ is hydrogen.

6. A compound as claimed in claim 1, 2 or 3 that is a sodium or potassium salt of a compound of formula (I) wherein R³ is hydrogen.

5

7. A compound as claimed in any preceding claim wherein R⁴ is CH(CH₃)₂.

8. A compound as claimed in any preceding claim wherein R⁵ is hydrogen.

10 9. A compound as claimed in any preceding claim wherein R⁵ is methyl.

10. A compound as claimed in any preceding claim wherein R⁶ and R⁷ are both hydrogen.

15 11. A process for preparing a compound as claimed in claim 1, the process comprising:

a. reacting a compound of formula (II):

(II)

with a compound of formula (III):

(III)

20 in the presence of NaBH(OAc)₃ or NaBH₃(CN) in a suitable solvent at a suitable temperature;

b. when R³ is alkyl or phenylalkyl, reacting a compound of formula (II) with a compound of formula (III), where R³ is alkyl or phenylalkyl, in the presence of NaBH(OAc)₃ in the presence of a suitable base, in a suitable solvent, at a suitable temperature;

25

- c. when R³ is hydrogen said compound may be converted to a compound of the invention where R³ is not hydrogen by a standard esterification or salt formation method well known in the art; or
- d. when R³ is not hydrogen said compound may be converted to a compound of the invention where R³ is hydrogen by a standard ester hydrolysis or acidification method well known in the art.

5

- 12. A pharmaceutical composition which comprises a compound of the formula (I), or a pharmaceutically acceptable salt thereof as claimed in claim 1, and a pharmaceutically acceptable adjuvant, diluent or carrier.

10

- 13. A compound of the formula (I), or a pharmaceutically acceptable salt thereof as claimed in claim 1, for use in therapy.

15

- 14. A compound of formula (I), or a pharmaceutically acceptable salt thereof as claimed in claim 1, in the manufacture of a medicament for use in therapy.

20

- 15. A method of treating a chemokine mediated disease state in a mammal suffering from, or at risk of, said disease, which comprises administering to a mammal in need of such treatment a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof as claimed in claim 1.

INTERNATIONAL SEARCH REPORTInternational application No.
PCT/SE2006/000611**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: 15
because they relate to subject matter not required to be searched by this Authority, namely:

Claim 15 relates to a method of treatment of the human body by therapy, as well as diagnostic methods /Rule 39.1(iv). Nevertheless, a search has been executed for this claim. The search has been based on the alleged effects of the compounds.
2. Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2006/000611

A. CLASSIFICATION OF SUBJECT MATTER

IPC: see extra sheet

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC: C07D, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-INTERNAL, WPI DATA, PAJ, CA, BIOSIS, EMBASE, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004087659 A1 (ASTRAZENECA AB), 14 October 2004 (14.10.2004), formula I --	1-15
X	WO 2004029041 A1 (ASTRAZENECA AB), 8 April 2004 (08.04.2004), claims 1-12 --	1-15
A	WO 2004085423 A1 (ASTRAZENECA AB), 7 October 2004 (07.10.2004), claims 1-11 --	1-15
A	WO 2004099144 A1 (ASTRAZENECA AB), 18 November 2004 (18.11.2004), formula I --	1-15

 Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier application or patent but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed
- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "&" document member of the same patent family

Date of the actual completion of the international search

20 July 2006

Date of mailing of the international search report

24-07-2006

Name and mailing address of the ISA/
Swedish Patent Office
Box 5055, S-102 42 STOCKHOLM
Facsimile No. +46 8 666 02 86

Authorized officer

Fernando Farieta/EÖ
Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No. PCT/SE2006/000611
--

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 1362857 A1 (DAINIPPON PHARMACEUTICAL CO., LTD.), 19 November 2003 (19.11.2003), formula I --	1-15
A	WO 02072570 A2 (SCHERING CORPORATION ET AL), 19 Sept 2002 (19.09.2002), claims 1-42 --	1-15
A	WO 03078395 A1 (ASTRAZENECA AB), 25 Sept 2003 (25.09.2003), formula I --	1-15
A	WO 0035877 A1 (DU PONT PHARMACEUTICALS COMPANY), 22 June 2000 (22.06.2000), formula I --	1-15
A	WO 0000488 A1 (SCHERING CORPORATION), 6 January 2000 (06.01.2000), formula I --	1-15
A	WO 9806697 A1 (SCHERING CORPORATION), 19 February 1998 (19.02.1998), formula I, claims 1, 7 -- -----	1-15

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2006/000611

International patent classification (IPC)

C07D 211/44 (2006.01)
A61K 31/445 (2006.01)
A61K 31/4545 (2006.01)
A61P 11/06 (2006.01)
C07D 211/26 (2006.01)
A61P 17/00 (2006.01)
A61P 19/00 (2006.01)

Download your patent documents at www.prv.se

The cited patent documents can be downloaded at www.prv.se by following the links:

- In English/Searches and advisory services/Cited documents (service in English) or
- e-tjänster/anfördta dokument (service in Swedish).

Use the application number as username.

The password is **FCRYRLVLCI**.

Paper copies can be ordered at a cost of 50 SEK per copy from PRV InterPat (telephone number 08-782 28 85).

Cited literature, if any, will be enclosed in paper form.

INTERNATIONAL SEARCH REPORT

Information on patent family members

04/03/2006

International application No.

PCT/SE2006/000611

WO	2004087659	A1	14/10/2004	AU	2003239002	A	00/00/0000
				AU	2004226010	A	14/10/2004
				BR	PI0409069	A	28/03/2006
				CA	2521073	A	14/10/2004
				EP	1512313	A	09/03/2005
				EP	1620400	A	01/02/2006
				MX	PA05010374	A	17/11/2005
				NO	20055068	A	02/01/2006
				SE	0300957	D	00/00/0000
				US	20060124635	A	15/06/2006
WO	2004029041	A1	08/04/2004	AU	2003259004	A	00/00/0000
				BR	0314688	A	02/08/2005
				CA	2497280	A	08/04/2004
				CN	1684952	A	19/10/2005
				EP	1546130	A	29/06/2005
				JP	2006503066	T	26/01/2006
				MX	PA05003007	A	22/06/2005
				NO	20051965	A	23/06/2005
				RU	2005105053	A	10/12/2005
				SE	0202838	D	00/00/0000
				US	20060040984	A	23/02/2006
				ZA	200502341	A	19/09/2005
WO	2004085423	A1	07/10/2004	AU	2003244276	A	00/00/0000
				CA	2485617	A	04/12/2003
				EP	1509331	A	02/03/2005
				EP	1611124	A	04/01/2006
				JP	2005527360	T	15/09/2005
				SE	0300850	D	00/00/0000
WO	2004099144	A1	18/11/2004	AU	2003267888	A	16/03/2005
				EP	1625114	A	15/02/2006
				SE	0301368	D	00/00/0000
				WO	2005022191	A	10/03/2005

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

04/03/2006

PCT/SE2006/000611

EP	1362857	A1	19/11/2003	SE	1362857	T3	
				AT	273304	T	15/08/2004
				AU	2003230245	A	00/00/0000
				BR	0309933	A	09/02/2005
				CA	2483368	A	27/11/2003
				CN	1653063	A	10/08/2005
				CZ	20041084	A	16/02/2005
				DE	60300021	D, T	08/09/2005
				ES	2227500	T	01/04/2005
				HK	1060118	A	04/03/2005
				JP	3643107	B	27/04/2005
				JP	2004043453	A	12/02/2004
				MX	PA04011332	A	14/02/2005
				NO	20045469	A	16/02/2005
				PL	372724	A	25/07/2005
				PT	1362857	T	30/11/2004
				RU	2004136853	A	27/06/2005
				SK	50192004	A	01/04/2005
				TR	200403020	T	23/05/2005
				US	6696468	B	24/02/2004
				US	20030216433	A	20/11/2003
				WO	03097638	A	27/11/2003
				ZA	200409035	A	12/07/2005

WO	02072570	A2	19/09/2002	CA	2440559	A	19/09/2002
				CN	1496362	A	12/05/2004
				EP	1373251	A	02/01/2004
				JP	2004520435	T	08/07/2004
				MX	PA03008356	A	11/12/2003
				US	6849621	B	01/02/2005
				US	20030109564	A	12/06/2003
				US	20050113383	A	26/05/2005

WO	03078395	A1	25/09/2003	AU	2003212770	A	00/00/0000
				CA	2443717	A	19/12/2002
				EP	1401285	A	31/03/2004
				EP	1487793	A	22/12/2004
				JP	2005526087	T	02/09/2005
				SE	0200844	D	00/00/0000
				US	20050176708	A	11/08/2005

WO	0035877	A1	22/06/2000	AU	2056800	A	03/07/2000
				CA	2347912	A	22/06/2000
				EP	1140834	A	10/10/2001
				US	6036057	A	14/03/2000
				US	6331545	B	18/12/2001
				US	6759411	B	06/07/2004
				US	20020119980	A	29/08/2002
				US	20040186097	A	23/09/2004

INTERNATIONAL SEARCH REPORT

Information on patent family members

04/03/2006

International application No.

PCT/SE2006/000611

WO	0000488	A1	06/01/2000	AT	272632	T	15/08/2004
				AU	756484	B	16/01/2003
				AU	1714400	A	05/06/2000
				AU	4820199	A	17/01/2000
				CA	2336000	A	06/01/2000
				CN	1146559	C	21/04/2004
				CN	1314905	A,T	26/09/2001
				DE	69919171	D,T	04/08/2005
				EP	1091956	A,B	18/04/2001
				EP	1131041	A	12/09/2001
				ES	2221399	T	16/12/2004
				HU	0104058	A	28/03/2002
				IL	140249	D	00/00/0000
				JP	3344997	B	18/11/2002
				JP	2002519349	T	02/07/2002
				JP	2002529487	T	10/09/2002
				NZ	508910	A	31/01/2003
				TW	474933	B	00/00/0000
				US	6607715	B	19/08/2003
				US	6638497	B	28/10/2003
				US	20030012763	A	16/01/2003
				WO	0028950	A	25/05/2000
				ZA	200007555	A	15/03/2002

WO	9806697	A1	19/02/1998	AT	297381	T	15/06/2005
				AU	732096	B	12/04/2001
				AU	3973297	A	06/03/1998
				BR	9711061	A	17/08/1999
				CA	2263167	A,C	19/02/1998
				CN	1155574	C	30/06/2004
				CN	1232453	A	20/10/1999
				CZ	9900433	A	14/07/1999
				DE	69733478	D,T	03/11/2005
				EP	0922029	A,B	16/06/1999
				ES	2241053	T	16/10/2005
				HU	9904363	A	28/11/2000
				IL	128524	D	00/00/0000
				JP	3390179	B	24/03/2003
				JP	2000500786	T	25/01/2000
				KR	2000029976	A	25/05/2000
				NO	990671	A	15/04/1999
				NZ	334017	A	28/04/2000
				PL	331536	A	19/07/1999
				SK	20199	A	13/03/2000
				TR	9900314	T	00/00/0000